REMARKS

This Response, filed in reply to the Office Action dated May 13, 2010, is believed to be fully responsive to each point of objection and rejection raised therein. Accordingly, favorable reconsideration on the merits is respectfully requested.

Claims 1-11, 14, 15 and 18-21 are all the claims pending in the application. Claims 1-11 are withdrawn from consideration as allegedly being directed to non-elected inventions. Claims 14, 15 and 18-21 are currently under examination, and are rejected.

No new matter is added by way of this response. Entry and consideration of this response are respectfully requested.

Claims 14, 15 and 18-20 are Not Obvious Under 35 U.S.C. § 103(a)

1. On page 3 of the Office Action, claims 14, 15 and 18-20 remain rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over EP 1174148A1 in view of U.S. 2003/0190316A1, essentially for the reasons set forth in the Office Action mailed August 25, 2009. For brevity, these reasons are not reiterated herein. The Examiner continues to find Applicants' traversal arguments, and evidence of unexpected results, unpersuasive, as follows.

First, in response to Applicants' arguments that the '148 publication teaches away from using a citrate buffer, due to its markedly inferior antibody stability vis-à-vis the phosphate buffer therein, the Examiner continues to assert that the data disclosed in Table 1 of the '148 publication would not have dissuaded those of ordinary skill in the art from employing the citrate buffer therein for stabilizing antibodies. Specifically, although the Examiner acknowledges Applicants' argument that Table 1 discloses markedly superior antibody stability using the

phosphate buffer vis-à-vis the citrate buffer, the Examiner again states on page 5, 2nd paragraph, of the Office Action that:

[f]rom … [T]able 1, it is evident that [the] phosphate buffer showed a higher stability at 40°C but citrate buffer has shown **higher** resistance at the heat treatment at 60°C. Note that the phosphate buffer has shown no degradation (100 to 100[%]) at 40°C but 19% degradation at 60°C (100 to 81[%], [T]able 1, lines 15-16) while [the] citrate buffer has shown only 4% degradation at 60°C (81-77[%], [T]able 1, lines 15-16) [Emphasis added].

Relying on the above interpretation of the data in Table 1 of the '148 publication, the Examiner maintains that those of ordinary skill in the art would readily have selected *the citrate buffer*, rather than the phosphate buffer, to enhance antibody stability at higher temperatures, because "the citrate buffer [allegedly is] more resistant to degradation at higher temperatures [than the phosphate buffer and is thus] a preferred buffer choice." *See* page 5, 2nd paragraph, of the outstanding Office Action. Moreover, on page 6 of the Office Action, the Examiner newly argues that, "regardless of whether the '148 publication teaches away from combining phosphate buffer and citrate," those of ordinary skill in the art would nevertheless readily combine the phosphate and citrate buffers of the '148 publication into a single formulation.[1] Motivation for combining the phosphate and citrate buffers is alleged to be found in claim 6 of the '148 publication, which discloses using "sodium phosphate and/or sodium citrate" as a buffer. *See* page 6, 1st paragraph, of the outstanding Office Action. Due to the open-ended transitional

[1] Applicants believe that the Examiner may have meant to state "[r]egardless of whether the '148 publication teaches away from combining citrate and glycine." This is because a teaching away from combining phosphate and citrate would be *highly relevant* as to whether those of ordinary skill in the art would have combined the phosphate and citrate buffers.

language recited in Claim 14 (*i.e.*, "comprising"), the Examiner asserts that the instant composition includes compositions containing sodium phosphate and sodium citrate."

Second, the Examiner continues to assert that Applicants' showing of unexpected results is not sufficient to rebut the obviousness rejection. In one aspect, the Examiner appears to maintain that the proffered evidence is not persuasive because it does not demonstrate unexpectedly superior suppression of chemical degradation, even though the Examiner acknowledges that such property is not actually required of the claimed composition. In a second aspect, the Examiner alleges that the data proffered to support unexpected results is not commensurate with claim scope because the Declaration evidence only demonstrates unexpected results of soluble association of antibody using a single species of antibody, *i.e.*, KM-871, and at a single pH, *i.e.*, pH 6.

Initially, Applicants note that the Examiner's response to Applicants' rebuttal arguments filed February 25, 2010, is essentially the same reasoning set forth in the previous Office Action. While Applicants previously informed the Examiner of the erroneous interpretation of the data in Table 1 of the '148 publication, and the Examiner's unfamiliarity of the relevant law pertaining to rebuttal of an obviousness rejection through a showing of unexpected results or properties, these arguments appear to have had little effect. However, in part because of the Examiner's erroneous interpretation of the experimental results in the '148 publication, Applicants maintain that the Examiner has yet to set forth a *prima facie* case of obviousness because the Examiner has failed to provide a credible reason that would have prompted a person of ordinary skill in the relevant field to specifically select the citrate buffer of the '148 publication, as *prima facie* obviousness would require. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007). As

Applicants have previously noted, the relied upon data in Table 1 actually teaches away from its use.

In addition, the Examiner's new line of argument, namely, that those of ordinary skill in the art, despite this teaching away, would nevertheless have possessed sufficient motivation to produce a buffer formulation containing citrate and phosphate upon reading claim 6 of the '148 publication, suffers from the same deficiencies. Because the phosphate buffer is both *more* stable at a higher temperature (*i.e.*, 60°C) and exhibits markedly *reduced* aggregation vis-à-vis the citrate buffer at this temperature, it is difficult to reconcile the Examiner's position on page 5, 2nd paragraph to page 6, 2nd paragraph of the Office Action, that those of ordinary skill in the art would have included the citrate buffer in a formulation together with the phosphate buffer, to provide enhanced resistance to degradation at high-temperature. Thus, this new argument by the Examiner is deficient because those of ordinary skill in the art would readily have recognized the inferiority of the citrate buffer vis-à-vis the phosphate buffer of the '148 publication for antibody stabilization at high temperature (*i.e.*, at 40°C and 60°C), such that they would not have expected any improvement in resistance to degradation when using this combination, but rather, would have expected the converse. That is, one of ordinary skill in the art would have expected such a combination to be less stable, because a portion of the relatively superior phosphate buffer would be replaced with the relatively inferior citrate buffer.

In addition, and independent of the above, Applicants have shown that the claimed composition possesses at least one unexpected property across the entire range of glycine and citrate concentrations (*i.e.*, unexpectedly superior suppression of soluble associations). Accordingly, any alleged *prima facie* case of obviousness asserted by the Examiner, is overcome.

Further, even though the Examiner appears to consider Applicants' proffered data unpersuasive, in part, because it allegedly does not demonstrate superior suppression of chemical degradation using the claimed composition, Applicants have already pointed out that unexpected superiority in just one property is sufficient to rebut a *prima facie* case of obviousness. *See In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987). In the present case, Applicants have shown that the claimed invention is at least unexpectedly superior for inhibition of soluble associations. The Examiner cites no controlling authority to the contrary to justify his position, nor are Applicants aware of any such contrary authority.

With regard to the Examiner's allegation that the proffered data is not persuasive because it is not commensurate with claim scope, it appears the Examiner is taking issue with the concentration and specificity of antibody tested, and the pH of the composition. In this respect, the Examiner appears to focus just on the Declaration in weighing the unexpected results, ignoring the wealth of experimental data in the specification as filed. However, the Examiner is not permitted to do so. Evidence of unexpected results or properties must be considered, *see In re Sullivan*, 498 F.3d 1345 (Fed. Cir. 2007), and from the totality of the record. *See In re Chu*, 66 F.3d 292, 298-99 (Fed. Cir. 1995). This is significant because the Examiner maintains that Applicants have only provided evidence for unexpected results with regard to a single antibody species. The Examiner's assertion is (incorrectly) based solely on the data in the Declaration. The Examiner's attention is respectfully directed to the specification which contains working examples demonstrating that the unexpected property of superior inhibition of soluble associations occurs with *different* antibodies, of *different* specificities. *See* Tables 3 and 9 which describe using anti-GD3 antibody and anti-CCR4 antibody, respectively. Thus, the Declaration evidence, in combination with the experimental data in the specification, is sufficient in itself.

Furthermore, the Examiner is reminded that the phrase "commensurate in scope," in the context of rebuttal of an obviousness rejection through a showing of unexpected results, requires only that the proffered evidence provides "a *reasonable* basis" for concluding that the untested embodiments encompassed by the claims would behave in the same manner as the tested embodiments. *See In re Lindner*, 457 F.2d 506, 508 (C.C.P.A. 1972). Accordingly, Applicants' showing that the unexpected property of superior inhibition of soluble associations is not limited to the KM-871 antibody, but is seen to the same magnitude with an entirely different antibody (*i.e.*, anti-CCR4 antibody), provides more than a "reasonable basis" from which those of ordinary skill in the art could conclude that the unexpected property would occur using the untested antibodies encompassed by the scope of the claims. Similarly, Applicants have also shown that neither the pH nor the antibody concentration used in the experiments described in the Declaration is critical for this unexpected property. For example, Table 10 in the specification as filed establishes that this unexpected property occurs to the same magnitude at a different antibody concentration (*i.e.*, 4mg/ml), and at a different pH (*i.e.*, pH 5.5). To this end, the disclosure in the specification provides a "reasonable basis" on which those of skill in the art could conclude that the untested embodiments encompassed by the claims would behave in the same manner as the tested embodiments, which is all the law requires. *Id.* Further, because evidence supporting such a "reasonable basis" has been provided, the rejection cannot be maintained absent some factual evidence, or sound scientific reasoning, establishing ***why*** those of ordinary skill in the art would not conclude that the unexpected result would occur across the scope of the claims in view of the data in the specification. At present, no such evidence exists. The Examiner has merely undertaken a mechanical comparison of the scope of the proffered

evidence to the scope of the claims, and having found them not to be identical, has maintained the rejection. This is not the law. *Id.*

Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claim 21 is Not Obvious Under 35 U.S.C. § 103(a)

2. On page 7 of the Office Action, the Examiner rejects Claim 21 under 35 U.S.C. § 103(a) as being unpatentable over EP 1174148 and U.S. Patent Application Pregrant Publication No. 2003/0190316, as applied above in the rejection of Claims 14-20, and further in view of U.S. Patent No. 6,488,930, of record.

3. On page 9 of the Office Action, the Examiner rejects Claim 21 under 35 U.S.C. § 103(a) as being unpatentable over EP 1174148 and U.S. Patent Application Pregrant Publication No. 2003/0190316, as applied above in the rejection of Claims 14-20, and further in view of U.S. Patent No. 6,437,098, of record.

In making these rejections, the Examiner contends that, at the time of the invention, those of ordinary skill in the art would readily have employed the stabilizing formulation taught by the '148 publication and the '316 publication, to stabilize a CCR4 humanized antibody, or a humanized ganglioside GD3 antibody, as allegedly disclosed by the '930 and '098 Patents, respectively.

Applicants strongly disagree, and assert that the rejections are deficient for the reasons discussed above for the '148 publication and '316 publication. Further, the '930 and '098 Patents merely disclose humanized anti-CCR4 and anti-GD3 antibodies, and do not disclose

glycine or citric acid based stabilization formulas, much less antibody solutions that inhibit soluble association of antibody.

Reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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